ZIKV is susceptible to the antiviral activity of IFN-α *in vitro* but fails to activate IFN response in human PBMC cultures

Biava M. ,Caglioti C., Castilletti C., Bordi L., Colavita F., Quartu S., Ippolito G., Capobianchi M.R., Lalle E.
National Institute for Infectious Diseases "L. Spallanzani", IRCCS - Rome, Italy

27th ECCMID
22 – 25 APRIL 2017
VIENNA, AUSTRIA
Reed Messe Vienna

Background

Interferons (IFN) are key cytokines with multifaceted antiviral and cell-modulatory properties, constituting the first line defense in the innate immune response. The activation of IFN response is triggered by the interaction of foreign material (PAMPs) with cell receptors (PRRs), and does not necessary require pathogen replication. Three IFN types are recognized, based on structural features, receptor usage, cellular source and biological activities. Since Zika virus (ZIKV) African and Asian lineages have been associated with a low IFN response[1], the purpose of this study was to explore the sensitivity of the two strains to different IFN types. In addition, we investigated their ability to induce IFN response and to replicate in PBMC from healthy donors.

Results (1)

Both African and contemporary Asian ZIKV lineages resulted sensitive to IFN-α2b activity but not to IFN-γ. In addition, no synergistic effect was observed with IFN-α + IFN-γ combination.

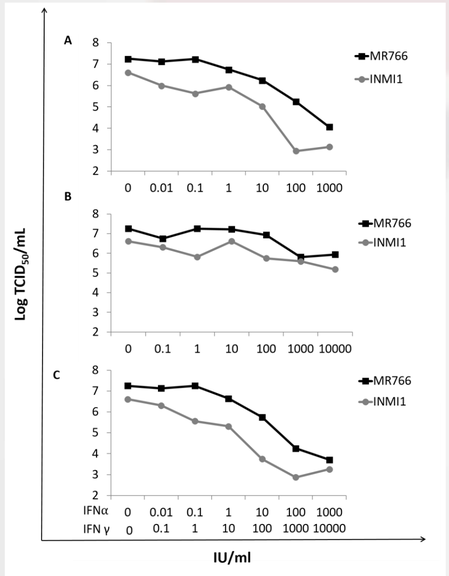

Fig 1. Dose-dependent inhibition of MR766 and INMI1 ZIKV replication by recombinant IFN-α, IFN-γ and IFN-α+IFN-γ. Vero E6 cells were treated for 18–20h with increasing amounts of IFN-2α (0.01-10^3IU/mL) or IFN-γ (0.1-10^4IU/mL), or a combination of them, then infected with either ZIKV African MR766 or the contemporary Asian INMI1 strain (MOI: 0.01), virus yield inhibition was measured after 24h of incubation. Yield decrease is expressed as Log $TCID_{50}$/mL. One representative experiment of three is shown. Symbols are specified in the panel. **A**: IFN-α antiviral activity; **B**: IFN-γ antiviral activity; **C**: IFN-α+ IFN-γ antiviral activity.

Results (2)

No activation of either type I, II or III was observed in PBMC from healthy donors at both mRNA and protein level after exposure to either ZIKV strains. Intriguingly, despite the lack of IFN induction, low MxA mRNA induction was observed only in PBMC infected with MR766 strain, peaking at 48 hpi **(Fig 2)**. Moreover, MR766 strain, but not INMI1 strain, was able to at least partially replicate in PBMC, as indicated by the increase in viral RNA at different times of infection **(Fig 3)**.

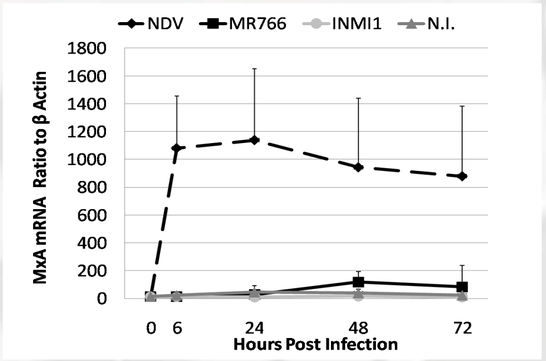

Fig 2. ZIKV African MR766 and Asian INMI1 strains MxA mRNA induction in PBMC. As a positive control for MxA mRNA induction, Newcastle Disease virus (NDV) was used in all the experiments. Average and standard deviation of three experiments is shown.

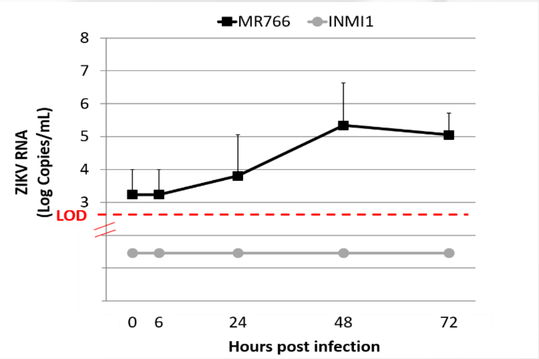

Fig 3. ZIKV African MR766 and Asian INMI1 strains total RNA replication kinetic in PBMC. Virus replication was assessed by RT-PCR, targeting NS5 gene[2]. Average and standard deviation of three experiments is shown.

Conclusions

- Both African and contemporary Asian ZIKV strains are sensitive to type I IFN, but not to type II IFN. Interestingly, neither of the two ZIKV strains is able to activate type I, II and III IFN response in PBMC from healthy donors
- Only MR766 is able to replicate in PBMC and to cause a transient and poor induction of MxA mRNA, whereas INMI1 lacks the ability to replicate and to induce the same antiviral response in PBMC
- The ability of ZIKV to infect dendritic cells among PBMC has been previously shown[3]. We hypothesize that the absence of a strong IFN response here reported may facilitate the viral dissemination and its ability to replicate in peripheral districts

References

[1] Kumar A, et al. (2016). Zika virus inhibits type-I interferon production and downstream signaling. EMBO Rep.
[2] Faye O, et al. (2013). Quantitative real-time PCR detection of Zika virus and evaluation with field-caught mosquitoes. Virol J.
[3] Hamel R, et al. (2015) Biology of Zika Virus Infection in Human Skin Cells. J Virol.